

## A comparison of human and animal botulism: a review

**E M R Critchley** DM FRCP    *Department of Neurology, Royal Preston Hospital, PO Box 66, Sharoe Green Lane, Preston PR2 4HT*

**Keywords:** botulism; preformed toxin; toxico-infection

### Summary

Botulism can arise from preformed toxin, wound infection or intestinal toxico-infection. All three forms can occur in humans as well as in animals. The examination of botulism in veterinary practice can alert the medical profession to the hazards which can occur with the introduction of dietary alterations and hermetic sealing of foodstuffs. There is also the possibility that the development of pica through lack of essential nutrients could lead to the ingestion of contaminated substances rendering the child (or even adult) susceptible to botulinum intoxication. A positive gain has been that research leading to the elimination of shaker foal disease has provided a comprehensive analysis of factors which may underline the risk of toxico-infection in infants<sup>12</sup>.

### Introduction

The rarity of human botulism contrasts with the frequent occurrence of animal botulism, involving tens of thousands of wild fowl each year, herds of wild and domesticated animals, and rare species raised in captivity. But there are indicators which suggest that unless today's rapid changes in dietary habits, food processing and presentation, are matched by increased vigilance into all aspects of food hygiene, food-borne disease, including botulism, may become a more common scourge. Whereas in the past human botulism was associated with inadequately cleaned, salted, smoked or dried fish or meat, the greatest risk nowadays arises from commercial or home-prepared condiments, vegetables, non-acid fruits and preserved raw fish. Plastic wrapped foods may warm and ferment in anaerobic conditions with survival of toxin at refrigerator temperatures<sup>1</sup>.

Human disease does not differ fundamentally in clinical features, ease of diagnosis, supportive laboratory testing, management or therapeutic measures from that seen in veterinary practice. For these reasons it is proposed to examine the circumstances and risk factors which result in outbreaks of botulism among animals.

*Clostridium botulinum* is a Gram-positive, anaerobic, rod-shaped bacillus widely distributed throughout the world in soil and marine deposits. Other telluric bacteria, such as *C. sporogenes*<sup>2</sup>, present in the same sediments inhibit germination and destroy any toxin produced. Nevertheless, the spores can survive for long periods in most environmental circumstances, withstanding dry heat but remaining susceptible to acidity, 8–10% saline solutions or moist heat. In its vegetative form the organism is an inhabitant of the alimentary canal of herbivores, thereby permitting its carriage to new locations. Such forms pose no threat to most adult animals.

*C. botulinum* appears to have a role at an early stage in the decomposition of animal, and occasionally vegetable, matter. In anaerobic conditions of increased alkalinity and temperature, spores will germinate with the release of toxin. The various strains of *C. botulinum* exhibit considerable polymorphism and differ widely in colony appearance, spore-forming capacity, ability to form one or more serologically distinct toxins, and in the state of synthesis of the toxin at the time of cell lysis. Thus some toxins are released as fully activated dichains whereas others require a further process of proteolytic nicking in vivo by intestinal enzymes to acquire full toxicity<sup>3,4</sup>. As other bacteria take over, survival of the spores is ensured but the toxin is thermo-labile and more rapidly inactivated as the pH rises. Nevertheless the greatest concentration of spores is to be found in carrion or spoiled foodstuffs, in larvae, grubs or other invertebrates feeding upon carrion, and in soil underlying carrion.

The differences between the serologically distinct toxins were exemplified experimentally by Miyazaki and Sakaguchi<sup>5</sup>. Preformed toxins of different types were administered to 2-week-old chickens intravenously, perorally, and intraduodenally to determine the minimum lethal dose. Intravenously toxin A was 1000 times more toxic than toxin C. When given intraduodenally, toxins C and A were equipotent despite the fact that 100 times more toxin C was absorbed and entered the systemic circulation. In vivo production of toxins (toxico-infection) was also examined. The oral administration of 10 *C. botulinum* spores of types A, C or D was sufficient to kill normal 2-week-old chickens. The spores germinated within the caecum with the production and absorption of toxin. If, however, the caecum was protected by ligation the chickens survived.

### Clinical features

The clinical features of botulism differ little between medical and veterinary practice. There are excellent accounts of botulism in horses<sup>6</sup>, cattle<sup>7</sup>, lions<sup>8</sup>, foxhounds<sup>9</sup> and baboons<sup>10</sup> with similar observations in sheep and pigs. Descriptions in wildfowl, chickens and turkeys<sup>11</sup> are also surprisingly similar. Animals may appear depressed, dull, reluctant to move and reluctant to take food. A few may show evidence of dribbling or dropping food from the mouth, abdominal distension, a low grade colic or even vomiting. The disease is not accompanied by fever but is characterized by a flaccid paralysis often starting in the hind-quarters with weakness, muscle tremors, stumbling and recumbency. The animal may be reluctant to rise, the lying posture may be abnormal and, on rising, the gait may be stilted and the hind limbs splayed and

ataxic. Weakness then progresses to the forequarters, head and neck. An abnormal posture of the head may be evident. Apparent lethargy, depression and dullness of expression may be the result of loss of tone around the eyes and mouth. The eyes may appear closed, the pupils dilated and pupillary reflexes sluggish. A diagnostic feature may be the ease with which the tongue can be grasped and pulled out of the mouth. Inability to swallow may be followed by paralysis of the thoracic muscles and laboured, diaphragmatic (abdominal) breathing. When an outbreak occurs acutely with a very brief incubation period the first evidence may be that a number of horses<sup>12,13</sup> or baboons<sup>10</sup> have died for no apparent reason. In avian outbreaks of botulism affecting ducks, chickens, turkeys, etc. the birds initially appear dull and reluctant to move. The eyes may be closed and the necks and wings stretched out with the legs tucked beneath them.

### Preformed toxins

Death of wildfowl from preformed toxin in shallow stagnant water usually occurs in conditions of drought and hot weather. Seepage of water from alkaline soils and thermal effluence as from power stations<sup>14</sup> enhance bacterial proliferation where there is oxygen depletion. Anaerobic conditions develop as the result of an overgrowth of pond weed and the presence of rotting vegetable and organic matter. A subsequent fall in temperature may allow the toxin to remain stable through the winter months causing further deaths among wild fowl in the following spring<sup>15</sup>. Decomposing carcasses in water are a potent source of intoxication and many deaths result from pecking at infected carrion.

Resistance to the effects of botulinum toxin, either innate or acquired, has been demonstrated in some carrion-eating mammals and birds. This is not invariably so: foxhounds<sup>9</sup> and lions<sup>8</sup> fed infected meat may develop botulism. Repeated infections may occur in susceptible animals<sup>16</sup>; and Greenwood<sup>8</sup> is convinced that unrecognized mild botulism may occur quite frequently in non-domestic carnivores, particularly if food hygiene is bad. Because of the extreme potency of *C. botulinum* toxin, it is likely that sub-lethal doses are too small to stimulate an immune response. However, with repeated mild infections it is possible that immunity does develop as is suggested by the presence of antitoxin in carrion-eating birds, such as the turkey vulture, fish-eating gulls and crows<sup>16</sup>. Vaccination with *C. botulinum* toxoid has been used successfully within herds of botulinum-affected cattle, and to protect racehorses and rare zoological specimens.

Destruction of livestock is usually associated with unnatural necrophagia, eg from the presence of rodent carcasses in fodder<sup>13</sup>. Trout have been infected in fish-farms after feeding with spoiled marine fish scraps<sup>16</sup>. Lamsieke among cattle in South Africa develops in times of drought when the parched grass is deficient in phosphorus. They develop a craving seeking to replenish the phosphorus from the shells of dead tortoises<sup>16</sup>. A similar condition, called Dry Bible, occurs among sheep and cattle in Western Australia. Malnourished and undernourished animals develop pica and are susceptible to botulism from carrion<sup>17</sup>. Cannibalism can occur among factory-farmed poultry associated with overcrowding, inadequate trough space and an unbalanced diet. Failure to remove dead birds may lead to an outbreak of botulism<sup>18</sup>.

Most outbreaks among animals are ascribed to infected foods, contaminated foods and unhygienic conditions<sup>10,11,18</sup>. Modern farming practices may also introduce botulism into carcass-free fodder. Grass harvested for silage is inevitably contaminated with soil<sup>7</sup>. Properly dried big bale silage is safe, but if damp, heavily moulded samples are hermetically sealed the pH can be as high as 8.5. In an alkaline pH with increasing temperature spores may germinate with the production of toxin<sup>13</sup>.

### Toxico-infection

#### Wound infection

Wound botulism, like tetanus, may result from deep contamination of wounds with the anaerobic germination of spores within the tissues of the host. Young males with compound fractures are particularly at risk. A comparable example from veterinary practice is provided by Bernard *et al.*<sup>6</sup> who describe botulism as a sequel to open castration performed in a barn at a local racetrack. Two weeks after surgery, the horse seemed stiff after galloping and was seen dropping food from its mouth. It became tremulous, the tone in the eyelids, tail, and tongue was markedly diminished, and the eyelids and tail could be lifted with minimal resistance. The tongue could be pulled out of the side of the mouth and the horse was unable to swallow. Under anaesthetic the scrotal incisions were reopened exposing a necrotic foul-smelling remnant of the spermatic cord. Debridement was performed and *C. botulinum* B isolated. Antitoxin and penicillin were given. The horse was fed gruel via a nasogastric tube. Hydration was monitored and oral toilet performed. The horse gradually improved over 10 days' hospitalization. Drainage from the surgical site ceased on day 4, muscle tone in the tongue and tail improved by day 5, and swallowing returned on day 8.

#### Intestinal infection

Adult toxico-infection is unusual but has occasionally been reported in association with achlorhydria, gastro-intestinal operations and stagnant loops of bowel. Infant botulism is well recognized and in many cases associated with ingestion of honey which may provide both the vehicle for the ingress of spores and a non-acid environment for their proliferation. Study of the intestinal micro-flora has suggested that there may be a delay in the establishment of normal flora, colonization by organisms that promote *C. botulinum*, the absence of organisms that inhibit *C. botulinum*, and a

Table 1. Optimum temperatures for germination and synthesis of toxins. State of activity of toxins *in vitro* before absorption and further *in vivo* activation by trypsin<sup>3,4</sup>

Toxins	Temperatures	State of activation	Those at risk
A	38-40°C	Fully synthesized	humans, animals
B		Nearly fully synthesized	humans, animals
E	33-35°C	Activated by trypsin	humans, animals
C 1+2	40-42°C	Partly activated by trypsin	animals only
D		Partly activated by trypsin	animals only

change in diet that results in constipation and stasis, allowing the germination and out-growth of spores<sup>19</sup>.

Toxico-infection is relatively rare among adult animals but in one outbreak of type *C. botulinum* in cattle-fed ensiled poultry litter<sup>20</sup> the outbreak was biphasic. Preformed toxin accounted for the acute onset of clinical signs within 72–96 h and the deaths occurring within 10 days. However, some animals only became affected about 2 weeks after having had access to the feed for 24 h. It was concluded that the ingestion of sublethal amounts of preformed toxin could serve to debilitate cattle transiently and possibly act as a prerequisite for in vivo toxin production from ingested spores.

The prime example of toxico-infection in animals is provided by shaker foal disease – a neuromuscular paralytic disease in foals prevalent in Central Kentucky. In 1967, McQuillen and Cantor confirmed the presynaptic nature of the neuro-muscular block (unpublished observation) but only later was the diagnosis of botulism established<sup>12</sup>. The disease most frequently developed in fast growing foals between 2 and 4 weeks old. At autopsy, necrotic areas were found in the skin, umbilicus, liver and especially in the gastric mucosa. It was thought that *C. botulinum* spores were ingested from contaminated soil and faecal material. Whereas in normal circumstances they are harmless, they are able to proliferate in necrotic gastric ulcers simulating wound botulism. Other factors appeared necessary for the disease to occur. The mares were usually fed on an excessively nutritious diet and produced an above average yield of milk with a high fat content. The disease commonly involved foals after periods of stress to lactating mares as a result of which the fat content of the milk contained an excessive amount of corticosteroids, thereby producing steroid ulcers. This sequence of events was reproduced and confirmed experimentally<sup>12</sup>.

Toxico-infection usually develops subacutely but Arnon *et al.*<sup>21</sup> have questioned whether botulism may occasionally be responsible for cases of sudden infant death. The likelihood of this possibility is increased by the fact that both experimentally and in humans cardiac dysrhythmias and congestive failure can occur with botulism<sup>22,23</sup>.

### Clinical considerations

The differential diagnosis includes cerebrovascular accidents, myasthenia gravis and polyradiculopathy, with the added possibilities of tick paralysis, organophosphate poisoning and adulteration of foods<sup>7,24</sup>. Inter- and intra-species variations in susceptibility to botulism remain largely unexplained: types C and D do not cause human disease, and in one outbreak of type C botulism only male turkeys were affected<sup>11</sup>. A shared carton of yoghurt caused botulism in two teenagers but not their cat<sup>25</sup> and contaminated chickens fed to lions, jaguars and coatis only affected the lions<sup>8</sup>.

The principles of treatment are the same in medical and veterinary practice. With the possible exception of antitoxin E<sup>26</sup>, the efficacy of antitoxins have not been established. Drugs which enhance neurotransmitter release, eg guanidines and aminopyridines are short acting and should not be used in the early stages unless further uptake of toxin is blocked by antitoxin administration. Difficulty in maintaining intravenous catheters when affected lions became at all active

precluded long-term infusion of 3,4-diaminopyridine which might have led to a more sustained response<sup>8</sup>.

The effects on the autonomic nervous system have not been analysed in animals, but there is some evidence of central nervous system involvement with perivascular haemorrhages in the corpus striatum, cerebellum and cerebrum<sup>27</sup>, and of convulsions in seemingly healthy mice after oral dosing<sup>24</sup>. Changes in peripheral nerve conduction<sup>25,28</sup> have also been found in 6 dogs found to have food-borne type C botulism<sup>29</sup>.

**Acknowledgments:** I am grateful to Professor M P McQuillen, Department of Neurology, University of Kentucky Medical Center, Lexington, USA, Professor R Jones, University of Liverpool and to Messrs D Gibbons and R Hogg MAFF, Veterinary Investigation Centre, Barton Hall, Preston for help with references.

### References

- 1 Thatcher FS, Robinson J, Endman I. The "vacuum pack" method of packaging foods in relation to the formation of the botulinum and staphylococcal toxins. *J Appl Bacteriol* 1962;25:120–4
- 2 Graham JM. Inhibition of *Clostridium botulinum* type C by bacteria isolated from mud. *J Appl Bacteriol* 1978;45:205–11
- 3 Sellin LC. The action of botulinum toxin at the neuromuscular junction. *Med Biol* 1981;59:11–20
- 4 Datta A, DasGupta BR. Botulinum neurotoxin types A, B & E: pH induced difference spectra. *Mol Cell Biochem* 1988;81:187–94
- 5 Miyazaki S, Sakaguchi G. Experimental botulism in chickens: the cecum as the site of production and absorption of botulinum toxin. *Jpn J Med Sci Biol* 1978;31:1–15
- 6 Bernard W, Divers TJ, Whitlock RH, Messick J, Tulleners E. Botulism as a sequel to open castration in a horse. *J Am Vet Med Assoc* 1987;191:73–4
- 7 Divers TJ, Bartholomew RC, Messick JB, Whitlock RH, Sweeney RW. *Clostridium botulinum* type B toxicosis in a herd of cattle and a group of mules. *J Am Vet Med Assoc* 1986;188:382–6
- 8 Greenwood AG. Diagnosis and treatment of botulism in lions. *Vet Rec* 1985;117:58–60
- 9 Blakemore WF, Rees-Evans ET, Wheeler PEG. Botulism in foxhounds. *Vet Rec* 1977;98:57–8
- 10 Lewis JCM, Smith GR, White VJ. An outbreak of botulism in captive hamadryas baboons (*Papio hamadryas*). *Vet Rec* 1990;103:216–17
- 11 Smart JL, Laing PW, Winkler CE. Type C botulism in intensively farmed turkeys. *Vet Rec* 1983;113:198–200
- 12 Swerczek TW. Toxicoinfective botulism in foals and adult horses. *J Vet Med Assoc* 1980;176:217–20
- 13 Ricketts SW, Greet TRC, Glyn PJ, *et al.* Thirteen cases of botulism in horses fed big bale silage. *Equine Vet J* 1984;16:515–18
- 14 Haagsma J. The etiology and epidemiology of botulism in waterfowl in the Netherlands. *Hydrobiol Bull* 1973;7:96–105
- 15 Graham JM, Smith GR, Borland ED, Macdonald JW. Avian botulism in winter and spring and the stability of *Clostridium botulinum* type C toxin. *Vet Rec* 1978;102:40–2
- 16 Smith GR. Botulism in waterfowl. *Symposia Zoo Soc London* 1982;50:97–119
- 17 Meyer KF. The status of botulism as a world health problem. *Bull World Health Organ* 1956;15:281–98
- 18 Blandford TB, Roberts TA. An outbreak of botulism in broiler chickens. *Vet Rec* 1970;87:258–61
- 19 Wilcke BW, Midura TF, Arnon SS. Quantitative evidence of intestinal colonisation by *Clostridium botulinum* in four cases of infant botulism. *J Infect Dis* 1980;141:419–23

- 20 Neill SD, McLoughlin MF, McIlroy SG. Type C botulism in cattle being fed ensiled poultry litter. *Vet Rec* 1989;124:558-60
- 21 Arnon SS, Midura TF, Damus K, Wood RM, Chin J. Intestinal infection and toxin production by *Clostridium botulinum* as one cause of sudden infant death syndrome. *Lancet* 1978;ii:1273-7
- 22 Vernant P. Formes cardiaques du botulisme. *Ann Microbiol (Inst Pasteur)* 1979;130A:141-2
- 23 Smith GR. Individual variation in botulism. *Br J Exp Pathol* 1986;67:617-21
- 24 Nafe LA. Selected neurotoxins. *Vet Clin North Am Small Anim Pract* 1988;18:593-604
- 25 Critchley EMR, Hayes PJ, Isaacs PET. Outbreak of

- botulism in North West England and Wales. June 1989. *Lancet* 1989;ii:849-53
- 26 Larson HE. Botulism. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine*, vol 1. Oxford University Press, 1984:230
- 27 Smith LDS. *Botulism, the organisms, its toxins, the disease*. Springfield, Illinois: CC Thomas, 1979
- 28 Sonnabend WF, Sonnabend OA, Grundler P, Katz E. Intestinal toxicoinfection by *Clostridium botulinum* type F in an adult. *Lancet* 1987;ii:357-60
- 29 van Ness JJ. Botulism and Guillain-Barré syndrome. *Lancet* 1987;ii:1033

(Accepted 6 November 1990)

## Forthcoming events

### Seventh Oswestry Spine Symposium

20-22 May 1991, Institute of Orthopaedics, Oswestry  
Further details from: Erica Wilkinson, Symposium Secretary, The Robert Jones & Agnes Hunt Orthopaedic and District Hospital, Oswestry, Shropshire SY10 7AG (Tel: 0691 655311 ext. 3392)

### Joint Meeting of The European Academy of Facial Surgery and The Swedish Society of Esthetic Surgery

23-24 May 1991, Goteborg, Sweden  
Further details from: M P Stearns, 97 Harley Street, London W1N 1DF (Tel: 071-487 4695)

### First North Sea Meeting on Venous Diseases

### Fourth Anglo-French Meeting on Phlebology

30 May-1 June 1991, Amsterdam, The Netherlands  
Further details from: Symposium Office, PO Box 39 5720 AA Astén, The Netherlands

### Strengthening Community Capacity to Prevent and Control Disease: Implementing Treatment and Prevention Programs for Children

12-14 June 1991, Carter Presidential Centre, Atlanta, Georgia  
Further details from: INMED, 103 Loudoun Street, SW, PO Box 4200, Leesburg, VA 22075, USA (Tel: 703 771 0011)

### Advanced Training Program in Biomedical Research Management

16-17 June 1991, Elsinore, Denmark  
Further details from: Prof. T Agersnap, Institution of Organization, Copenhagen School of Economics, Blågårdsgade 23 B, DK-2200 Copenhagen N, Denmark (Tel: 45 31 37 05 55; Fax: 45 42 80 57 50)

### Thyroid '91

4-5 July 1991, Newcastle upon Tyne  
Further details from: Dr Petros Perros, Department of Medicine, The Medical School, University of Newcastle, Newcastle NE2 4HH

### Institute of Medical Ethics Conference on The Ethics of Using Animals in Biomedical Research

9-11 July 1991, Birmingham University, UK  
Further details from: The Conference Secretary, Department of Biomedical Science and Biomedical Ethics, The Medical School, Birmingham B15 2TT, UK

### Techniques and Applications of Molecular Biology: A Course for Medical Practitioners

15-18 July 1991, University of Warwick  
(Closing date: 27 May 1991)  
Further details from: Dr Rachel Strachan (Short Courses), Department of Biological Sciences, University of Warwick, Coventry CV4 7AL (Tel: 0203 523523 ext. 3540; Fax: 0203 523701)

### Pre-Congress Course for Physiotherapists

23-26 July 1991, Institute of Orthopaedics, Oswestry  
Further details from: (see entry for 20-22 May 1991)

### 3rd Annual Meeting of the British Sleep Society

1-3 September 1991, Worcester College, Oxford  
Further details from: Dr J Stradling, Osler Chest Unit, Churchill Hospital, Headington, Oxford OX3 7LJ (Tel: 0865 225236; Fax 0865 225221)

### 7th IUVDT Regional Conference on Sexually Transmitted Diseases

5-7 September 1991, Kuala Lumpur, Malaysia  
Further details from: Conference Secretariat, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur, Malaysia (Tel: 03 7502264; Fax: 603 7557740)

### Dynamic Axial Fixation Course

18-20 September 1991, Institute of Orthopaedics, Oswestry  
Further details from: (see entry for 20-22 May 1991)

### Look After Your Heart International Conference: Collaboration, Co-Operation and Community Participation

19-20 September 1991, London  
Further details from: Judy Berry, Health Education Authority, Hamilton House, Mabledon Place, London WC1H 9TX (Tel: 071-383 3833; Fax 071-387 0550)

### Monitoring of Orthopaedic Implant Biomaterials: Microelectronics Challenge

25-28 September 1991, Brussels  
Further details from: F Burny, Service Orthopedie-Traumatologie, Université Libre de Bruxelles, Route de Lennik 808, B 1070 Bruxelles, Belgium (Tel: 2-526 36 45; Fax: 2-520 35 56)

### Autumn Meeting of the British Association of Oral and Maxillofacial Surgeons

27-29 September 1991, Harrogate Conference Centre  
Further details from: John C Lowry, Honorary Secretary, British Association of Oral and Maxillofacial Surgeons, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN

### 3rd International Conference on SLE

13-15 April 1992, Queen Elizabeth II Conference Centre, London  
Further details from: Dr Graham Hughes or Mrs Denzil Fletcher, Rheumatology Department, St Thomas' Hospital, London SE1 7EH (Tel and Fax: 071-633 9422)

### Principles of Colon and Rectal Surgery

9-12 October 1991, University of Minnesota, Minneapolis  
Further details from: Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55455, USA (Tel: 612 626 7600)